

Levetiracetam in Men With Epilepsy: Testosterone Is Left Alone But Sperm Count Is Paramount

Effects of Levetiracetam Monotherapy on Sperm Parameters and Sex Hormones: Data From Newly Diagnosed Patients With Epilepsy.

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PURPOSE: Epilepsy has an impact on the reproductive system. Males with epilepsy have lower fertility rates, hypo-sexuality and reduced potency compared with the general population. Anti-epileptic drugs and epilepsy itself are thought to be responsible for this reduced fertility. LEV is a second-generation anti-epileptic agent with low incidences of both adverse effects and drug–drug interactions. In this study, we have investigated the effects of LEV treatment on sex hormones and sperm parameters in newly diagnosed epilepsy patients. **METHODS:** We recruited 26 males with newly diagnosed epilepsy and introduced LEV monotherapy. Patients were divided into two groups depending on whether they had partial or generalized seizures. We acquired the results of pre- and post-treatment sperm analyses and serum sex hormone levels. We also recorded the maximum dose, daily dose and treatment duration for each individual. Pre- and posttreatment comparisons and correlations between both sperm and sex hormone parameters and both treatment duration and dose were determined. **RESULTS:** Pre- and post-treatment sex hormone levels were not significantly different. The total sperm count, percentage of normal morphology and functional sperm count tested after treatment were significantly lower in both groups compared with pre-treatment values ($p < 0.05$). There was a moderate correlation between daily dose and reduction in functional sperm count ($r: 0.41$, $p: 0.034$). **CONCLUSIONS:** Our findings confirm that LEV treatment of newly diagnosed epilepsy patients decreases sperm parameters without altering sex hormone levels. Our results may guide the choice of antiepileptic drug treatment among men with epilepsy.

Commentary

I can clearly recall the first patient who asked me if his anti-seizure medications would affect his sperm count or fertility. Despite being steeped in information about women with epilepsy and the teratogenic effects of antiepileptic medications, I realized that I was woefully unprepared to answer his question. We discussed that antiseizure medications could cause erectile dysfunction, but I told him that I didn't think they would affect his sperm counts. I let him know that I would look it up and get back to him. The next day, after finding several reports of decreased sperm counts and motility in patients taking carbamazepine, I called him back to share my newfound knowledge, and wondered how I could have gotten through most of my epilepsy fellowship training without knowing this.

The effects of antiseizure medications in men, as in women, can be complex. Men with epilepsy have higher rates of sexual dysfunction and reduced fertility. Gastaut and Collumb (1) noted a pervasive hyposexuality in their patients with temporal lobe epilepsy. The reduced fertility in men with epilepsy was thought to derive in part from psychosocial influ-

ences, but to have a larger contribution of biological drivers, including the epilepsy itself and the antiseizure medications used to treat it.

As in women with epilepsy, seizures can disrupt the pulsatile secretion of gonadotropin-releasing hormone (GnRH) from the hypothalamus, with downstream effects on luteinizing hormone (LH) and follicle stimulating hormone (FSH) release from the pituitary. In men, LH and FSH act on the testes with resulting effects on secondary sex characteristics and fertility. LH acts on the Leydig cells of the testes to signal testosterone production, while FSH acts primarily on Sertoli cells, which direct sperm production. Studies that have included untreated men with epilepsy have shown lower volume of seminal fluid, lower sperm concentrations, higher rates of morphologically abnormal sperm, and lower sperm counts than healthy controls, suggesting that epilepsy itself may play role in producing some of these abnormalities (2).

However, an independent role of antiseizure medications is also clear. Enzyme-inducing antiepileptic drugs (EIAEDs) are known to produce hormonal changes in men, including increased production of sex hormone binding globulin (SHBG) leading to lower levels of free (biologically active) testosterone (3). Additionally, treatment with EIAEDs has been associated with decreased sperm concentrations, more frequent sperm morphological abnormalities, and reduced motility (4). For



years it has also been clear that some of the effect of antiseizure medications is independent of hepatic enzyme induction; studies of the effect of valproate on measures of sperm number, morphology, and function have produced similar findings (5). In case reports, the resolution of laboratory abnormalities and infertility following a change in antiseizure medication has provided compelling evidence of specific AED effects (6, 7).

The mechanism by which older AEDs produce these changes has been debated. Both valproate and the EIAEDs have effects on endogenous hormones, which may lead to secondary effects on spermatogenesis. A direct toxic effect on sperm production has also been postulated. Study of newer AEDs that have few hormonal interactions could be informative. Is it reasonable to think that they might have fewer effects on male fertility? If one of my male patients taking levetiracetam asked me the same question that my patient did years ago (will my medication affect my sperm count or fertility?), I would have been uncertain how to answer until recently.

Ceylan and coworkers recently published work that will help us counsel patients and that may contain clues to the answers for some underlying biological questions. They studied a relatively pure culture of 26 men with new-onset epilepsy, with a mean age of 28.6 years (range, 18–43), who had normal neuroimaging studies, and who were free of other confounds such as other major systemic disease, hormonal treatment, or testicular abnormalities. Approximately one-third were described as having focal seizures and two-thirds generalized seizures. The decision to study only patients with new-onset epilepsy was helpful in eliminating lingering effects of prior treatment with other AEDs and the effects of chronic epilepsy.

All subjects underwent an assessment of hormones (LH, FSH, prolactin, testosterone, estradiol) and sperm parameters (sperm count, morphology, and motility) before and after a mean of 13.7 weeks of treatment with levetiracetam. The results showed dissociation between hormonal function and sperm parameters. There were no significant changes in any of the measured hormone levels in these levetiracetam-treated men, in contradistinction to studies of the older AEDs, and as might be anticipated by its pharmacokinetics. Yet measures of sperm count, morphology, and motility all worsened compared with pretreatment values, suggesting a more direct effect of the drug on spermatogenesis, though the mechanism remains unclear. There was evidence of a dose-response relationship, with lower sperm parameters associated with higher dose levetiracetam treatment. The magnitude of the effect (~10–20% reduction in sperm parameters), while not dramatic,

and less that reported in some studies of older AEDs, nonetheless meets World Health Organization infertility criteria and is potentially clinically significant (8).

These findings had been foreshadowed by the work of Xiaotian et al. (9), whose study of the effects of several AEDs, including levetiracetam, on male reproductive function reached similar conclusions.

More studies of this kind assessing newer AEDs are needed. This study reported short-term outcomes, and the effects of long-term use of levetiracetam are not well understood. There are little or no data on many other newer AEDs. Study of these newer drugs would provide the epilepsy community with information about the effects of specific AEDs to guide counseling about the relative risks of decreased fertility in men with epilepsy.

by David Spencer, MD

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